Cannabidiol for Treatment-Resistant Anxiety Disorders in Young People: An Open-Label Trial

Maximus Berger, MD, PhD[a,b,*]; Emily Li, BPsychPsy[a,b]; Simon Rice, PhD[a,b]; Christopher G. Davey, MBBS, PhD[c]; Aswin Ratheesh, MBBS, PhD[a,b]; Sophie Adams, MBBS, PhD[a,b]; Henry Jackson, PhD[d]; Sarah Hetrick, PhD[a,b]; Alexandra Parker, PhD[a,b,e]; Tim Spelman, PhD[f]; Richard Kevin, PhD[g,h]; Iain S. McGregor, PhD[g,h]; Patrick McGorry, MBBS, PhD[a,b]; and G. Paul Amminger, MD, PhD[a,b]

ABSTRACT

Background: Treatment resistance is a significant problem among young people experiencing moderate-to-severe anxiety, affecting nearly half of all patients. This study investigated the safety and efficacy of cannabidiol (CBD), a non-intoxicating component of *Cannabis sativa*, for anxiety disorders in young people who previously failed to respond to standard treatment.

Methods: In this open-label trial, 31 young people aged 12–25 years with a *DSM-5* anxiety disorder and no clinical improvement despite treatment with cognitive-behavioral therapy and/or antidepressant medication were enrolled between May 16, 2018, and June 28, 2019. All participants received add-on CBD for 12 weeks on a fixed-flexible schedule titrated up to 800 mg/d. The primary outcome was improvement in anxiety severity, measured with the Overall Anxiety Severity and Impairment Scale (OASIS), at week 12. Secondary outcomes included comorbid depressive symptoms, Clinical Global Impressions scale (CGI) score, and social and occupational functioning.

Results: Mean (SD) OASIS scores decreased from 10.8 (3.8) at baseline to 6.3 (4.5) at week 12, corresponding to a −42.6% reduction ($P < .0001$). Depressive symptoms ($P < .0001$), CGI-Severity scale scores ($P = .0008$), and functioning ($P = .04$) improved significantly. Adverse events were reported in 25 (80.6%) of 31 participants and included fatigue, low mood, and hot flushes or cold chills. There were no serious and/or unexpected adverse events.

Conclusions: These findings suggest that CBD can reduce anxiety severity and has an adequate safety profile in young people with treatment-resistant anxiety disorders. Randomized controlled trials are needed to confirm the efficacy and longer-term safety of this compound.

Trial Registration: New Zealand Clinical Trials Registry (ANZCTR) identifier: ACTRN12617000825358

J Clin Psychiatry 2022;83(5):21m14130

To cite: Berger M, Li E, Rice S, et al. Cannabidiol for treatment-resistant anxiety disorders in young people: an open-label trial. *J Clin Psychiatry.* 2022;83(5):21m14130.

To share: https://doi.org/10.4088/JCP.21m14130

[a]Orygen, Melbourne, Australia

[b]Centre for Youth Mental Health, University of Melbourne, Melbourne, Australia

[c]Department of Psychiatry, University of Melbourne, Melbourne, Australia

[d]Melbourne School of Psychological Sciences, University of Melbourne, Melbourne, Australia

[e]Institute for Health and Sport, Victoria University, Melbourne, Australia

[f]Burnet Institute, Melbourne, Australia

[g]Lambert Initiative for Cannabinoid Therapeutics, University of Sydney, Sydney, Australia

[h]School of Psychology, University of Sydney, Sydney, Australia

**Corresponding author:* Dr Maximus Berger, 35 Poplar Rd, Melbourne, VIC 3052, Australia (maximus.berger@unimelb.edu.au).

Anxiety disorders are among the most common mental disorders affecting young people globally, with a lifetime prevalence of 15%–20% in children and adolescents.[1] They typically have their onset early in life and are leading causes of disability.[2–4] Current treatment guidelines typically recommend cognitive-behavioral therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs) as first-line treatments for anxiety disorders. However, while these treatments are effective for many patients,[5] only 55%–60% of adolescents with anxiety disorders achieve remission.[6–9]

Cannabidiol (CBD), a cannabinoid found in the plant *Cannabis sativa*, has received significant attention in recent years due to its emerging putative physical and mental health benefits. Unlike tetrahydrocannabinol (THC), CBD is devoid of propsychotic effects.[10,11] Recent randomized controlled trials (RCT) have found that CBD has a generally favorable side-effect profile compared to many psychotropic drugs.[12] RCTs that have been conducted to date have shown that CBD may be effective at improving symptoms of psychosis[13,14] and treatment-refractory childhood epilepsies.[15,16] Pharmaceutical CBD (eg, Epidiolex) has been approved to treat Lennox-Gastaut syndrome and Dravet syndrome in several jurisdictions, including in the Unites States. However, evidence regarding the safety and efficacy of CBD for most mental disorders is currently insufficient to make clear recommendations regarding its use.[17]

Reductions in anxiety severity after administration of CBD have been observed in animal studies[11] and case reports[18–20] as well as in small human studies.[21–23] A recent small randomized-controlled trial in 37 adolescents with social anxiety disorder[23] demonstrated that a 4-week intervention with CBD 300 mg/d led to modest but significant reductions in anxiety severity. While the anxiolytic effects of CBD appear promising, its acceptability and safety for young patients with anxiety disorders are unclear, as are the duration of treatment and the optimum dose needed to achieve clinical response

Clinical Points

- Treatment resistance represents a significant challenge in the treatment of anxiety disorders in young people, with nearly half of all patients not achieving remission despite evidence-based treatment with selective serotonin reuptake inhibitors and/or cognitive-behavioral therapy.
- Anxiety severity decreased significantly in young people with treatment-refractory anxiety who received cannabidiol in daily doses between 400 mg and 800 mg for 12 weeks. Randomized clinical trials are required to confirm the efficacy of cannabidiol for anxiety disorders.
- Consistent with previous clinical trials, cannabidiol demonstrated an acceptable safety profile in this trial.

and the efficacy of CBD for patients who have previously not responded to established treatments. Therefore, the aim of this trial was to test the safety and the efficacy of CBD as an adjunctive treatment for anxiety disorders in young people aged 12–25 years with anxiety disorders who do not respond to standard treatment.

PATIENTS AND METHODS

Study Design and Patients

The present study was an open-label, single-arm Phase II trial in patients with anxiety disorders who previously did not respond to standard treatment with CBT and/or antidepressant medication. There was no control group. Patients, investigators, and clinicians were not blind to the intervention. All participants received the study intervention. Study participants were recruited from all patients with anxiety disorders who attended a primary mental health care service in Melbourne (headspace) between May 2018 and July 2019. headspace Australia is a national network of more than 100 primary mental health care services for young people aged 12–25 years across Australia with approximately 405,000 patient contacts in 2020, of which 32% were due to anxiety disorders.[24,25] To be eligible, participants had to be aged between 12 and 25 years (inclusive), have been diagnosed with a *DSM-5* anxiety disorder (ascertained with the Structured Clinical Interview for *DSM-5* [SCID-5]), and have experienced no improvement in anxiety severity in the current episode of care despite standard treatment with CBT and/or antidepressant medication (operationalized as a score of 3 or higher on the Clinical Global Impressions–Improvement scale [CGI-I]). The participants were also required to be able to provide informed consent and have sufficient fluency in English. Exclusion criteria were a *DSM-5* schizophrenia spectrum disorder, delusional disorder, bipolar I disorder, or substance/medication-induced psychotic disorder; prior sensitivity or allergy to CBD or any cannabis-derived product; current treatment with antipsychotic medication, anxiolytic medication, or mood stabilizer or any medication that either interacts with the metabolism of CBD or is affected by CBD and in the view of the study doctor cannot be coadministered safely; pregnancy, lactation, or, if sexually active, no effective contraception; hematologic findings that indicate a medically significant liver, thyroid, or other condition; acute or unstable systemic medical disorder; psychiatric condition due to a medical condition; acute suicidality; previous or current severe drug or severe alcohol dependence; or severe disturbance, such that the person is unable to comply with either the requirements of informed consent or the treatment protocol. Antidepressant medication was permitted if the participant had been on a stable dose for a minimum of 6 weeks prior to enrollment. The numbers of participants screened, excluded, and enrolled are shown in Supplementary Figure 1.

The trial was sponsored by Orygen and reviewed and approved by an independent human research ethics committee (Bellberry Ltd.; HREC2017-02-107). The study was approved under the Clinical Trial Notification Scheme by the Therapeutic Goods Administration (TGA) and registered with the Australian and New Zealand Clinical Trials Registry (ANZCTR) on 06/06/2017 with the registration identifier ACTRN12617000825358.

Procedures and Intervention

Written informed consent was obtained from all participants prior to commencing study-related procedures. Parent or legal guardian consent was obtained in addition to participant assent for participants aged 17 years or younger. All participants were invited to attend a screening interview with a researcher during which the presence of all inclusion and absence of all exclusion criteria were established using a structured interview. The presence of a *DSM-5* anxiety disorder was ascertained with the SCID-5, which was administered by a trained research assistant prior to enrollment. The participant's treating psychologist, who was not part of the study team, provided a CGI-I rating to determine clinical improvement. After enrollment, participants received the study medication and attended study visits at weeks 4, 8, 12, and 26. In addition, blood draws were completed every 4 weeks, and participants were seen by a study physician at 4-weekly intervals until week 12 to monitor the safety of the study drug. All participants continued treatment as usual throughout the trial, consisting of CBT sessions every 2 weeks in addition to antidepressant treatment and/or psychosocial care as determined by their psychiatrist.

All participants received CBD for 12 weeks, followed by gradual weaning for 1 week. CBD was administered in the form of oral capsules, each containing 200 mg high-purity (>99.9%) CBD and the inactive ingredient Softisan 379 (Trigal Pharma GmbH; Vienna, Austria). Dosing followed a fixed-flexible schedule, starting with 200 mg/d for all participants. Doses were subsequently increased in 200-mg increments if participants did not show clinically meaningful improvement (operationalized as a score of 3 or higher on the CGI-I). The maximum doses were 400 mg/d at week 1, 600 mg/d at week 4, and 800 mg/d at week 8. Treatment adherence was confirmed by pill count.

Biomarker Analysis

Fasting blood samples were collected every 4 weeks at baseline, week 4, week 8, and week 12 between 8:00 AM and 10:00 AM. Routine clinical safety blood tests included a full blood count, comprehensive metabolic panel, lipid panel, and thyroid function test. CBD concentrations in plasma and plasma concentrations of antidepressant drugs were quantified with liquid chromatography (LC)–tandem mass spectrometry (LC–MS/MS) at the University of Sydney using validated protocols reported elsewhere.[26,27]

Outcome Measures

The primary endpoint was improvement in anxiety severity at week 12, measured on the Overall Anxiety Severity and Impairment Scale (OASIS). The OASIS is a 5-item transdiagnostic self-report measure that can be used to assess severity and impairment associated with any anxiety disorder. It has excellent test-retest reliability, good convergent and discriminant validity,[28,29] and strong sensitivity to change.[30] Secondary outcomes were safety and tolerability of CBD, assessed as the frequencies of adverse events, serious adverse events and withdrawals and discontinuations due to adverse events, study completion rate, and routine clinical blood tests completed in 4-weekly intervals. Adverse events and serious adverse events were recorded at each study visit using open-ended questions and reviewed by a study physician. Secondary outcomes also included absence of a diagnosis of an anxiety disorder, as diagnosed by the SCID-5[31]; the CGI-I[32]; the Hamilton Anxiety Rating Scale (HARS)[33]; the Quick Inventory Depression Symptomatology, Adolescent Version (QIDS-A_{17})[34]; the Social and Occupational Functional Assessment Scale (SOFAS)[35]; and the Cannabis Withdrawal Scale (CWS)[36] to assess symptoms of withdrawal once the study medication was ceased. Research assessments were completed by trained research assistants who were not involved in the clinical care of research participants.

Statistical Analysis

The sample size for this pilot trial was pre-determined based on feasibility and anticipated attrition rather than statistical power. Safety analyses were carried out on all enrolled participants (n = 31). Efficacy analyses were carried out on an intention-to-treat basis, restricted to all participants who completed baseline and at least one post-baseline observation (n = 30). Raw scores of outcome measures were calculated, including change in scores from baseline to week 12 and from baseline to the 26-week follow-up. Effect sizes were calculated using the formula $(Mean_{post} - Mean_{pre})/ SD_{diff.,}$. For change in symptom and functioning scores, we used linear mixed-effects models with restricted maximum likelihood estimator and unstructured covariance matrix. All models included random intercepts for participants and fixed effects for time, age, and gender. CGI-I scores and changes in CGI–Severity of Illness (CGI-S) ratings were compared with the Wilcoxon signed rank test. In a post hoc analysis, non-parametric correlation coefficients and linear and logistic regression models were used to examine the effect of antidepressant medication, maximum daily dose of CBD, and plasma CBD levels on adverse events and on the efficacy of CBD. A *P* value below .05 was considered significant. All analyses were performed in Stata 15.1 (Stata Corp; College Station, Texas).

Table 1. Baseline Characteristics of Study Participants[a]

Variable	Participants Included in Safety Analysis (n = 31)	Participants Included in Efficacy Analysis (n = 30)
Age, mean (SD), y	21.1 (2.7)	21.1 (2.7)
Gender		
Female	18 (58.1)	18 (60.0)
Male	11 (35.5)	11 (36.7)
Non-binary	2 (6.5)	1 (3.3)
Relationship status		
Single/never married	20 (64.5)	19 (63.3)
Partnered	10 (32.3)	10 (33.3)
Missing	1 (3.2)	1 (3.3)
Education and employment[b]		
Full-time education or employment	16 (51.6)	15 (50.0)
Part-time education or employment	6 (19.4)	6 (20.0)
Non-standard work	1 (3.2)	1 (3.3)
Not in education and unemployed	7 (22.6)	7 (23.3)
Diagnosis		
Generalized anxiety disorder	3 (9.7)	3 (10.0)
Social anxiety disorder	15 (48.4)	14 (46.7)
Panic disorder	0 (0.0)	0 (0.0)
Specific phobia	1 (3.2)	1 (3.3)
Generalized anxiety disorder + social anxiety disorder	6 (19.4)	6 (20.0)
Panic disorder + social anxiety disorder	4 (12.9)	4 (13.3)
Generalized anxiety disorder + social anxiety disorder + panic disorder	2 (6.5)	2 (6.7)
Comorbid major depressive disorder	11 (35.5)	11 (36.7)
Duration of treatment episode in months, median (IQR)	25.5 (10.75–38.25)	24 (10.00–36.25)
No. of previous antidepressant medications, median (IQR)	2 (1–2.75)	2 (1–3)
Duration of previous antidepressant treatment, median (IQR), mo	19 (8–31)	20 (7.75–31.25)
Current antidepressant medication	21 (67.7)	20 (66.7)
SSRI	16 (51.6)	15 (50.0)
SNRI	3 (9.7)	3 (10.0)
Tricyclic antidepressants	1 (3.2)	1 (3.3)
Tetracyclic antidepressants	6 (19.4)	6 (20.0)
Fluoxetine	5 (16.1)	4 (13.3)
Citalopram	1 (3.2)	1 (3.3)
Escitalopram	5 (16.1)	5 (16.7)
Sertraline	5 (16.1)	5 (16.7)
Mirtazapine	6 (19.4)	6 (20.0)
Venlafaxine	2 (6.5)	2 (6.7)
Desvenlafaxine	1 (3.2)	1 (3.3)
Dosulepin	1 (3.2)	1 (3.3)

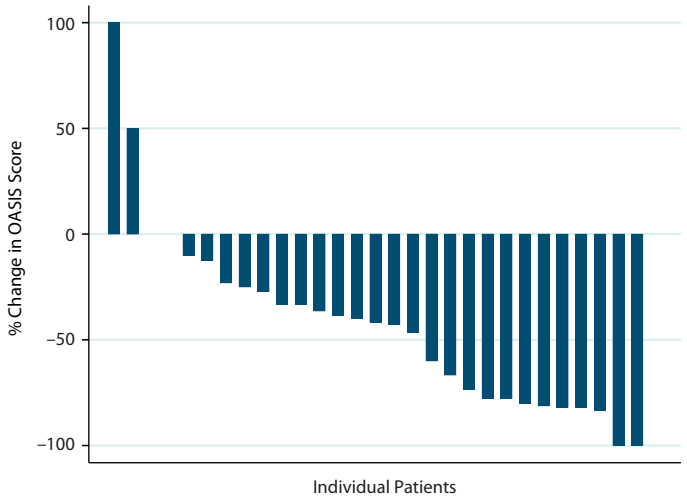
[a]Values are shown as n (%) unless otherwise noted.
[b]Among patients included in the efficacy analysis, 1 partipant (3.3%) did not have data available and/or declined to answer.
Abbreviations: IQR = interquartile range, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

RESULTS

Patient Characteristics

A total of 31 participants were enrolled between May 16, 2018, and June 28, 2019 (Supplementary Figure 1). Of 70 patients initially approached, 37 provided informed consent and 31

Figure 1. Percentage Change in OASIS Score of Patients Included in the Efficacy Analysis (n = 30) From Baseline to Week 12[a]



[a]Percentage changes are shown for each patient, ordered from greatest increase to greatest decrease.
Abbreviation: OASIS = Overall Anxiety Severity and Impairment Scale.

were eligible for the trial following a screening interview and blood test. All 31 participants were included in the safety analysis and 30 (96.8%) of 31 participants were included in the efficacy analysis. One participant withdrew prior to the first post-baseline study visit, and another participant withdrew prior to the primary endpoint. Reasons for withdrawal included skin rash deemed possibly related to the study medication (n = 1) and inability to meet the time commitment required for the study (n = 1). Anxiety disorder diagnoses at baseline included social anxiety disorder, generalized anxiety disorder, panic disorder, and specific phobias. The median duration of prior treatment as usual for anxiety disorders was 25.5 months. Twenty-one participants were prescribed antidepressants in addition to CBT with a median duration of 19 months and a median number of 2 medication changes due to lack of efficacy or side effects. Participant characteristics for the safety and efficacy analysis group are reported in Table 1.

Efficacy Analysis

Nineteen participants were titrated to the maximum CBD dose of 800 mg/d. Ten participants received a lower maximum dose of 600 mg/d (n = 9) or 400 mg/d (n = 1) at week 12 based on treatment response and/or adverse events. Two participants who withdrew prior to week 12 received lower maximum doses of 200 mg/d. None of the study participants continued to use CBD between end of treatment (week 12) and the follow-up visit (week 26).

In the intention-to-treat analysis, anxiety severity decreased significantly from baseline to week 12 (Table 2). The mean (SD) change in OASIS score was −4.6 (4.2) points, or −42.6%, from baseline (Cohen $d = -1.07$). Twelve (40%) of 30 participants had a reduction of at least 50% in OASIS scores by week 12, and 18 of 30 participants had a reduction of at least 33% (Figure 1). Analysis of the secondary endpoints showed that HARS scores similarly decreased from baseline (mean [SD] decrease: −11.1 [10.6] points, or 50.2% (Cohen $d = -1.00$; Table 2, Figure 2B). We also observed a mean (SD) reduction in depressive symptom severity of −3.5 (4.2) points, or 29.9%, on the QIDS-A_{17} (Cohen $d = -0.83$; Table 2, Figure 2C). Social and occupational functioning improved by a mean (SD) of 6.4 (8.9) points, or 11.3%, on the SOFAS (Cohen $d = 0.69$; Table 2, Figure 2D). Improvements in anxiety and depressive symptoms and social and occupational functioning were not sustained after 6 months (n = 13), which included a 14-week follow-up phase during which treatment was not controlled.

Analysis of CGI ratings showed that 26 (86.7%) of 30 participants had improved and 16 (53.3%) of 30 participants had substantially improved by week 12. By the end of treatment, the number of participants rated as markedly or severely ill had decreased from 17 (56.7%) to 5 (16.7%) (Table 3).

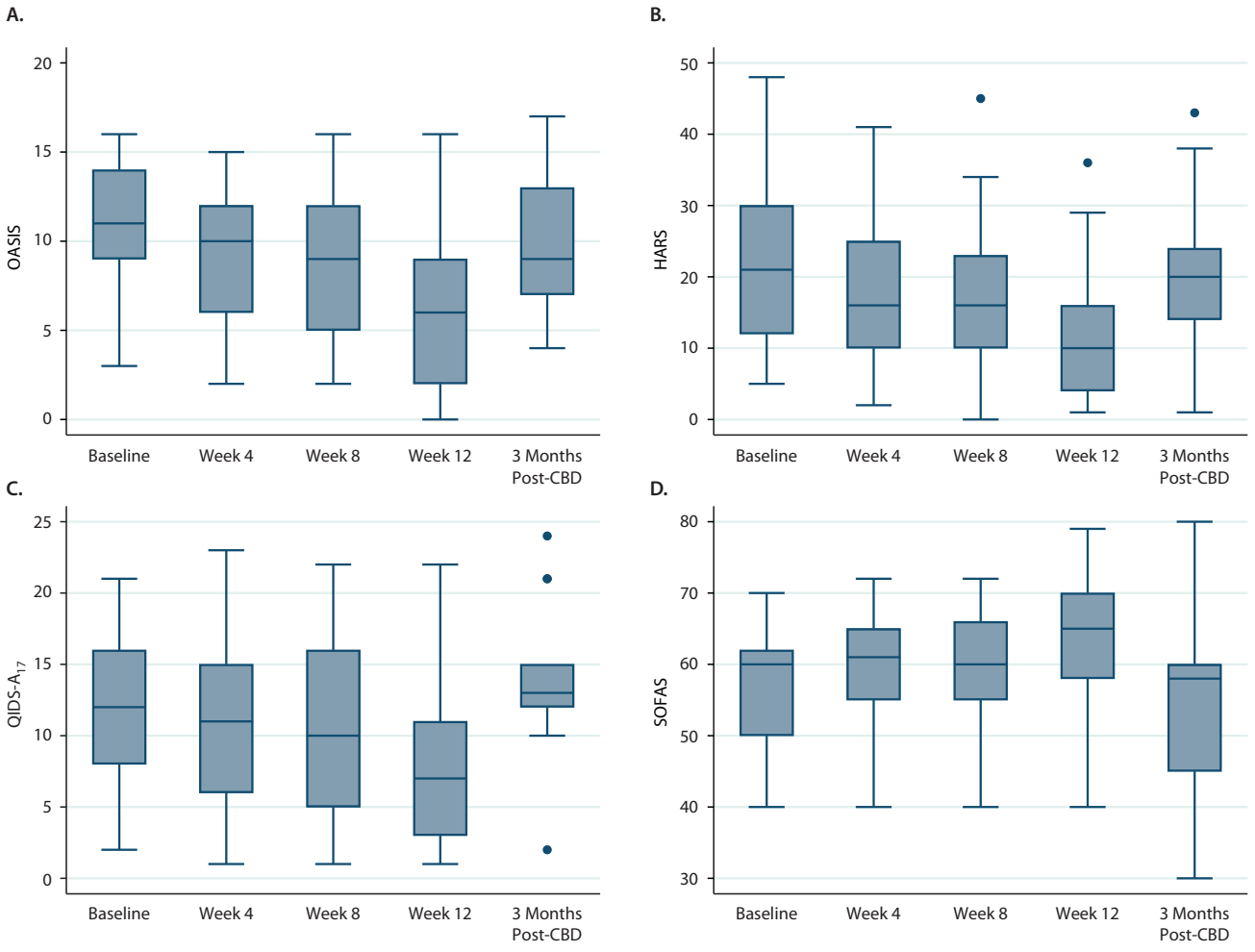
At baseline, CBD was not detectable in plasma in any of the participants. Mean (SD) plasma CBD concentrations increased to 43.5 (5.7) ng/mL at week 4, 74.1 (7.7) ng/mL at week 8, and 68.7 (8.4) ng/mL at week 12. The maximum plasma CBD concentration in participants for whom CBD was titrated up to 600 mg/d did not differ significantly from that in those who received a maximum CBD dose of 800 mg/d (Supplementary Figure 2); however, participants who received a maximum dose of 600 mg/d had higher plasma concentrations at week 4 than participants who received up to 800 mg/d. Results of the post hoc analysis examining the relationship between plasma

Table 2. Changes in Symptom Severity and Functioning From Baseline to end of Treatment and 6-Month Follow-Up

Measure	Baseline, Mean (SD)	Week 4, Mean (SD)	Week 8, Mean (SD)	Week 12, Mean (SD)	Week 26,[a] Mean (SD)	Mean Change (Baseline to Week 12) Mean (SD)	%	Cohen *d*	Mean Change (Baseline to Week 26) Mean (SD)	%	Cohen *d*	Linear Mixed-Effects Model,[b] *P* Value
OASIS	10.8 (3.8)	9.0 (3.8)	8.3 (4.3)	6.3 (4.5)	9.8 (4.1)	−4.6 (4.2)	−42.6	−1.07	−2.7 (3.1)	−18.8	−0.32	< .0001
HARS	21.9 (11.4)	18.2 (10.8)	17.1 (11.8)	11.3 (9.1)	20.5 (12.0)	−11.1 (10.6)	−50.7	−1.00	−5.8 (9.6)	−16.1	−0.15	< .0001
QIDS-A_{17}	11.7 (5.3)	11.0 (6.2)	10.7 (6.0)	8.2 (6.3)	14.1 (5.6)	−3.5 (4.2)	−29.9	−0.83	−0.6 (4.9)	−1.1	0.49	< .0001
SOFAS	56.7 (8.9)	58.8 (9.1)	60.2 (8.8)	62.8 (10.8)	54.2 (12.4)	+6.4 (8.9)	+11.3	0.69	+1.3 (9.9)	+3.2	−0.25	.04

[a]n = 13.
[b]Baseline until end-of-treatment (primary outcome).
Abbreviations: HARS = Hamilton Anxiety Rating Scale; OASIS = Overall Anxiety and Impairment Scale; QIDS-A_{17} = Quick Inventory of Depressive Symptoms, Adolescent Version; SOFAS = Social and Occupational Functioning Scale.

Figure 2. Primary and Secondary Outcome Measures of Patients Included in the Efficacy Analysis (n = 30) at Baseline and at Week 4, Week 8, and Week 12 and 3 Months Post-CBD[a]



[a]Monthly changes in (A) OASIS scores, (B) HARS scores, (C) QIDS-A_{17} scores, and (D) SOFAS scores. Boxplots show median values and 25th and 75th percentiles. Whiskers represent the 25th percentile − 1.5 × IQR and the 75th percentile + 1.5 × IQR. Dots represent values above or below the upper and lower adjacent value, respectively.

Abbreviations: CBD = cannabidiol; HARS = Hamilton Anxiety Rating Scale; IQR = interquartile range; OASIS = Overall Anxiety Severity and Impairment Scale; QIDS-A_{17} = Quick Inventory of Depressive Symtomatology, Adolescent Version; SOFAS = Social and Occupational Functioning Assessment Scale.

concentrations of CBD and outcome showed that plasma CBD concentrations at week 12 ($r = -0.14$, $P = .46$) and the maximum CBD plasma concentrations during the treatment period ($r = -0.004$, $P = .83$) were not correlated with the mean reduction in OASIS scores. We further examined whether the observed reduction in anxiety severity was dependent on antidepressant medication and found a significant interaction between antidepressant medication and change in OASIS score, with participants not prescribed antidepressant medication having greater reductions ($P = .02$). However, the mean (SD) improvement in OASIS scores from baseline to week 12 was significant in participants who were prescribed antidepressants (−3.5 [5.3], $P = .003$) as well as those not taking antidepressants (−5.6 [2.8], $P < .001$).

Safety Analysis

Adverse events were reported by 25 (80.6%) of 31 participants included in the safety analysis (Supplementary Table 1). Adverse events deemed related or possibly related to the study drug by the study physician were reported by 19 (61.3%) of 31 participants and included fatigue, low mood, increased or decreased appetite, drowsiness, nausea, diarrhea, dry mouth, insomnia, and hot flushes or cold chills. No serious adverse events or suspected unexpected serious adverse reactions were observed. There were no clinically significant changes to red or white blood cell counts, renal function, or liver function. One request for withdrawal was due to an adverse event (skin rash deemed possibly related to CBD). All adverse events were mild or moderate in severity and resolved spontaneously during the study.

A post hoc analysis showed that the number of adverse events was unrelated to the maximum CBD dose achieved during the trial (Spearman $\rho = -0.03$, $P = .88$), plasma concentrations of CBD at week 12 (Spearman $\rho = -0.26$, $P = .17$), or the maximum plasma concentrations of CBD during the trial (Spearman $\rho = -0.09$, $P = .63$). Patients

Table 3. Changes in Global Clinical Impressions Scale Scores From Baseline to End of Treatment[a]

CGI Score Category	Baseline (n = 30)	Week 4 (n = 26)	Week 8 (n = 28)	Week 12 (n = 29)	Baseline vs Week 12
CGI-S					*P* = .0008
Not ill	0 (0)	0 (0)	0 (0)	0 (0)	
Borderline ill	0 (0)	1 (3.8)	0 (0)	0 (0)	
Mildly ill	2 (6.7)	3 (11.5)	6 (21.4)	7 (24.1)	
Moderately ill	11 (3.7)	12 (46.2)	13 (46.4)	17 (58.6)	
Markedly ill	14 (46.7)	10 (38.5)	7 (25.0)	4 (13.8)	
Severely ill	3 (10.0)	0 (0)	2 (7.1)	1 (3.5)	
Extremely ill	0 (0)	0 (0)	0 (0)	0 (0)	
CGI-I					*P* < .0001
Very much	0 (0)	0 (0)	0 (0)	2 (6.9)	
Much	0 (0)	2 (7.7)	9 (32.1)	14 (48.3)	
Minimal	17 (56.7)	12 (46.2)	9 (32.1)	10 (34.5)	
No change	11 (36.7)	10 (38.5)	8 (23.6)	3 (10.3)	
Minimal worse	2 (6.7)	2 (7.7)	2 (7.1)	0 (0)	
Much worse	0 (0)	0 (0)	0 (0)	0 (0)	
Very much worse	0 (0)	0 (0)	0 (0)	0 (0)	

[a]Values are shown as n (%) unless otherwise noted.
Abbreviations: CGI-I = Clinical Global Impressions–Improvement scale, CGI-S = Clinical Global Impressions–Severity of Illness scale.

who were prescribed antidepressants were more likely to experience at least one adverse event (OR = 6.4; 95% CI, 1.16–35.44; *P* = .03). While plasma CBD concentrations were unrelated to the risk of experiencing adverse events among all participants who were prescribed antidepressants (OR = 1.01; 95% CI, 0.97–1.05; *P* = .62), 5 of 6 participants taking citalopram or escitalopram showed increases in the plasma concentrations of the two drugs after 12 weeks' treatment with CBD.

DISCUSSION

The aim of this open-label trial was to test the safety and efficacy of CBD for treatment resistant anxiety disorders in people aged 12–25 years. In the intention-to-treat analysis, we observed a statistically significant reduction in anxiety severity after 12 weeks of treatment with CBD. The mean reduction in OASIS score at week 12 of 4.6 points (42.6%) corresponds to a clinically meaningful effect in this group of young people who have previously not responded to standard treatment for anxiety disorders. Approximately 40% of all participants experienced a 50% reduction in OASIS score, and two-thirds experienced a 33% reduction. The improvement in anxiety severity was confirmed by secondary outcome measures (HARS) and supported by the CGI-I rating, which showed that clinically significant improvement was evident to the clinicians in 26 of 30 participants. CBD has previously been found to reduce anxiety symptoms in case reports of patients with anxiety disorders,[18–20] observational studies in patients with primary anxiety, or anxiety related to other illnesses[37] and experimental studies in patients,[21,22] healthy volunteers,[11] and adolescents with social anxiety.[23] Given that the patients included in our trial were some of the most severe and treatment resistant and had significant functional impairment and multiple failed treatment attempts, the reduction in anxiety severity observed here suggests that CBD has clinically meaningful anxiolytic effects.

The mechanisms by which CBD may exert beneficial effects on anxiety are not completely understood but likely include effects on the CB_1 and 5-HT_{1A} receptors and TRPV1, anti-inflammatory and antioxidant effects, and increases in endocannabinoid tone.[11,38] In imaging studies, CBD reduced activation of limbic and paralimbic brain areas during anxiety in patients with social anxiety disorder.[21] With a mechanism of action that is apparently different from that of SSRIs commonly used to treat anxiety disorders, CBD may represent a new class of drug for anxiety disorders. Future studies should further explore the mechanism of action of CBD, its interactions with psychotropic medication, and potential synergistic effects with psychological therapies.

CBD demonstrated an acceptable safety profile in our trial, with no serious adverse events reported and no clinically significant deviations to blood cell counts. While a majority of participants reported some adverse events deemed possibly related to the intervention, the majority of these were mild and resolved spontaneously. The most common adverse events were fatigue, low mood, and hot flushes or cold chills. One of 2 withdrawals in this trial was due an adverse event (skin rash). Overall, the adverse events observed in our trial are similar to those in other trials of CBD in different populations.[39,40] A noteworthy finding from this trial was that adverse events were more common in participants who were concurrently taking antidepressants. CBD is an inhibitor of the CYP3A4, CYP2C19, and other cytochrome P450 enzymes involved in the metabolism of psychotropic drugs.[41] Several antidepressants, including fluoxetine, venlafaxine, and escitalopram, are substrates of these enzymes.[42] To test the hypothesis that CBD increases plasma levels of antidepressants, we examined whether plasma levels changed during the trial. Among 5 of 6 participants taking escitalopram, plasma levels were increased throughout the trial relative to baseline.[26] This finding may reflect the particular reliance of escitalopram, relative to other antidepressants, on metabolism via CYP2C19, which is strongly inhibited by CBD.[43] Of note, participants were required to remain on a stable dose of antidepressant medication for 6 weeks before enrollment and throughout the trial. There was no evidence for a relationship between plasma CBD levels and the frequency of adverse events. Overall, results from this trial confirm the notion that CBD has a favorable safety profile and demonstrate that CBD is generally well tolerated in a population of young people with anxiety disorders.

Our trial has several limitations that need to be considered when interpreting these findings. First, our trial was open-label and uncontrolled. Therefore, causal inferences about the efficacy of CBD relative to other influences cannot be made. Second, the prominent role of CBD in the media and the fact that we included a treatment-resistant population increase the risk of expectancy bias in our trial. To reduce this risk, the trial accepted only referrals from clinicians (and not self-referrals). Moreover, failed

treatment attempts in the past may reduce expectancy bias in this population. Strengths of the trial include the use of high-purity (>99.5%) CBD, the stringent eligibility criteria, the dose-escalation protocol, and the analysis of plasma CBD levels. The age range of the participants included in this trial is representative of the primary mental health infrastructure provided by headspace Australia for young people in Australia.

Since our trial included the titration period and because the strongest effects were observed in the last 4 weeks of treatment, it is possible that longer treatment at an effective dose or more rapid titration would have led to even greater improvements. Based on our criteria to increase the dose until efficacy was noted on the CGI, the majority of participants were titrated to the maximum dose of 800 mg/d and a smaller proportion to 600 mg/d or 400 mg/d. Because our trial also included a background intervention of CBT and/or antidepressant medication and close monitoring by researchers and study doctors, the relative contribution of these components needs to be determined in future trials with appropriate control conditions. However, we found no evidence that the reduction in anxiety severity was dependent on antidepressant medication use in this trial. The observation that there were no sustained benefits of CBD 3 months after the end of the intervention further supports the notion that treatment as usual did not explain the observed benefits during the 12-week intervention. While concomitant recreational cannabis use might complicate the therapeutic actions of CBD on anxiety and depression, only 2 of the 30 participants displayed detectable concentrations of THC or THC-COOH in their plasma during the trial. It is therefore unlikely that cannabis use contributed to or diminished the observed effect.

To our knowledge, this clinical trial of CBD is the first in young people with anxiety disorders for whom established treatments are not effective. The findings of this trial suggest that further investigation of CBD for anxiety in conjunction with usual care is warranted.

Submitted: June 15, 2021; accepted February 15, 2022.

Published online: August 3, 2022.

Author contributions: G.P.A., P.M., and M.B. were responsible for the study design, obtaining funding, and drafting the study protocol. As Principal Investigator, G.P.A. had overall responsibility for the implementation of the study. E.L. and M.B. were responsible for project management and data collection. G.P.A. oversaw the medical management of the study participants. R.K. and I.S.M. analyzed cannabinoid and antidepressant plasma concentrations. G.P.A. and M.B. developed the statistical analysis plan, and M.B. analyzed the data. M.B. wrote the first draft of the manuscript. All authors contributed to the final version of the manuscript.

Relevant financial relationships: The authors declare that there is no biomedical or financial conflict of interest.

Funding/support: The study was funded by a grant from the Lambert Initiative for Cannabinoid Therapeutics (Sydney, NSW, Australia). M.B. was supported by a Rapid Applied Research Translation Fellowship awarded by the Medical Research Future Fund (Canberra, ACT, Australia). G.P.A. was supported by an NHMRC Senior Research Fellowship (1080963).

Role of the sponsor: The supporting sources had no involvement in the writing of the article.

Previous presentation: An interim analysis of this trial was presented at the Annual Conference of the Society for Mental Health Research (SMHR); Melbourne, Australia; November 27–29, 2019.

Acknowledgments: We would like to thank the participants and their families. We would also like to acknowledge the technical assistance of Rebecca Vogel (Lambert Initiative for Cannabinoid Therapeutics, University of Sydney) and Melissa Benson, PhD (Lambert Initiative for Cannabinoid Therapeutics, University of Sydney), and the contributions of the late Associate Professor David Allsop, PhD (Lambert Initiative for Cannabinoid Therapeutics, University of Sydney), to this trial. Dr Benson and Ms Vogel report no conflict of interest in relation to this trial.

Supplementary material: Available at Psychiatrist.com.

REFERENCES

1. Beesdo K, Knappe S, Pine DS. Anxiety and anxiety disorders in children and adolescents: developmental issues and implications for DSM-V. *Psychiatr Clin North Am*. 2009;32(3):483–524.
2. Ginsburg GS, Becker EM, Keeton CP, et al. Naturalistic follow-up of youths treated for pediatric anxiety disorders. *JAMA Psychiatry*. 2014;71(3):310–318.
3. Kessler RC, Ruscio AM, Shear K, et al. Epidemiology of anxiety disorders. *Curr Top Behav Neurosci*. 2010;2:21–35.
4. Copeland WE, Angold A, Shanahan L, et al. Longitudinal patterns of anxiety from childhood to adulthood: the Great Smoky Mountains Study. *J Am Acad Child Adolesc Psychiatry*. 2014;53(1):21–33.
5. Cuijpers P, Cristea IA, Karyotaki E, et al. How effective are cognitive behavior therapies for major depression and anxiety disorders? A meta-analytic update of the evidence. *World Psychiatry*. 2016;15(3):245–258.
6. James AC, James G, Cowdrey FA, et al. Cognitive behavioural therapy for anxiety disorders in children and adolescents. *Cochrane Database Syst Rev*. 2015;(2):CD004690.
7. Strawn JR, Welge JA, Wehry AM, et al. Efficacy and tolerability of antidepressants in pediatric anxiety disorders: a systematic review and meta-analysis. *Depress Anxiety*. 2015;32(3):149–157.
8. Baldwin D, Woods R, Lawson R, et al. Efficacy of drug treatments for generalised anxiety disorder: systematic review and meta-analysis. *BMJ*. 2011;342(mar11 1):d1199.
9. Dobson ET, Bloch MH, Strawn JR. Efficacy and tolerability of pharmacotherapy for pediatric anxiety disorders: a network meta-analysis. *J Clin Psychiatry*. 2019;80(1):17r12064.
10. Bhattacharyya S, Morrison PD, Fusar-Poli P, et al. Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. *Neuropsychopharmacology*. 2010;35(3):764–774.
11. Blessing EM, Steenkamp MM, Manzanares J, et al. Cannabidiol as a potential treatment for anxiety disorders. *Neurotherapeutics*. 2015;12(4):825–836.
12. Chesney E, Oliver D, Green A, et al. Adverse effects of cannabidiol: a systematic review and meta-analysis of randomized clinical trials. *Neuropsychopharmacology*. 2020;45(11):1799–1806.
13. McGuire P, Robson P, Cubala WJ, et al. Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: a multicenter randomized controlled trial. *Am J Psychiatry*. 2018;175(3):225–231.
14. Leweke FM, Piomelli D, Pahlisch F, et al. Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Transl Psychiatry*. 2012;2(3):e94.
15. Devinsky O, Cross JH, Laux L, et al; Cannabidiol in Dravet Syndrome Study Group. Trial of cannabidiol for drug-resistant seizures in the Dravet Syndrome. *N Engl J Med*. 2017;376(21):2011–2020.
16. Devinsky O, Marsh E, Friedman D, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. *Lancet Neurol*. 2016;15(3):270–278.
17. Black N, Stockings E, Campbell G, et al. Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta-analysis. *Lancet Psychiatry*. 2019;6(12):995–1010.
18. Klier CM, de Gier C, Felnhofer A, et al. A case report of cannabidiol treatment of a Crohn's disease patient with anxiety disorder. *J Clin Psychopharmacol*. 2020;40(1):90–92.
19. Shannon S, Lewis N, Lee H, et al. *Cannabidiol in Anxiety and Sleep: A Large Case Series*. Permanente J.; 2019:23.
20. Shannon S, Opila-Lehman J. Effectiveness of cannabidiol oil for pediatric anxiety and insomnia as part of posttraumatic stress disorder: a case report. *Perm J*. 2016;20(4):16–005.
21. Crippa JA, Derenusson GN, Ferrari TB, et al. Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report. *J Psychopharmacol*. 2011;25(1):121–130.
22. Bergamaschi MM, Queiroz RH, Chagas MH, et al. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naïve

social phobia patients. *Neuropsychopharmacology*. 2011;36(6):1219–1226.
23. Masataka N. Anxiolytic effects of repeated cannabidiol treatment in teenagers with social anxiety disorders. *Front Psychol*. 2019;10:2466.
24. McGorry PD, Goldstone SD, Parker AG, et al. Cultures for mental health care of young people: an Australian blueprint for reform. *Lancet Psychiatry*. 2014;1(7):559–568.
25. Headspace Australia. Annual Report 2019–2020; 2020.
26. Anderson LL, Doohan PT, Oldfield L, et al. Citalopram and cannabidiol: in vitro and in vivo evidence of pharmacokinetic interactions relevant to the treatment of anxiety disorders in young people. *J Clin Psychopharmacol*. 2021;41(5):525–533.
27. Kevin RC, Vogel R, Doohan P, et al. A validated method for the simultaneous quantification of CBD, THC, and their metabolites in human plasma, and application to plasma samples from an oral CBD open label trial. *Drug Test Anal*. 2021;13(3):614–627.
28. Norman SB, Campbell-Sills L, Hitchcock CA, et al. Psychometrics of a brief measure of anxiety to detect severity and impairment: the Overall Anxiety Severity and Impairment Scale (OASIS). *J Psychiatr Res*. 2011;45(2):262–268.
29. Norman SB, Cissell SH, Means-Christensen AJ, et al. Development and validation of an Overall Anxiety Severity and Impairment Scale (OASIS). *Depress Anxiety*. 2006;23(4):245–249.
30. Moore SA, Welch SS, Michonski J, et al. Psychometric evaluation of the Overall Anxiety Severity And Impairment Scale (OASIS) in individuals seeking outpatient specialty treatment for anxiety-related disorders. *J Affect Disord*. 2015;175:463–470.
31. American Psychiatric Association. *Diagnostic and Statistical Manual for Mental Disorders*. Fifth Edition. Washington, DC: 2013.
32. Guy W. *ECDEU Assessment Manual for Psychopharmacology*. US Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs; 1976.
33. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol*. 1959;32(1):50–55.
34. Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry*. 2003;54(5):573–583.
35. Morosini PL, Magliano L, Brambilla L, et al. Development, reliability and acceptability of a new version of the *DSM-IV* Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. *Acta Psychiatr Scand*. 2000;101(4):323–329.
36. Allsop DJ, Norberg MM, Copeland J, et al. The Cannabis Withdrawal Scale development: patterns and predictors of cannabis withdrawal and distress. *Drug Alcohol Depend*. 2011;119(1–2):123–129.
37. Gulbransen G, Xu W, Arroll B. Cannabidiol prescription in clinical practice: an audit on the first 400 patients in New Zealand. *BJGP Open*. 2020;4(1):bjgpopen20X101010.
38. Russo EB, Burnett A, Hall B, et al. Agonistic properties of cannabidiol at 5-HT1a receptors. *Neurochem Res*. 2005;30(8):1037–1043.
39. Amminger GP, Berger M, Rice SM, et al. Novel biotherapies are needed in youth mental health. *Australas Psychiatry*. 2017;25(2):117–120.
40. Iffland K, Grotenhermen F. An update on safety and side effects of cannabidiol: a review of clinical data and relevant animal studies. *Cannabis Cannabinoid Res*. 2017;2(1):139–154.
41. Brown JD, Winterstein AG. Potential adverse drug events and drug-drug interactions with medical and consumer Cannabidiol (CBD) use. *J Clin Med*. 2019;8(7):989.
42. Richelson E. Pharmacokinetic drug interactions of new antidepressants: a review of the effects on the metabolism of other drugs. *Mayo Clin Proc*. 1997;72(9):835–847.
43. Huezo-Diaz P, Perroud N, Spencer EP, et al. CYP2C19 genotype predicts steady state escitalopram concentration in GENDEP. *J Psychopharmacol*. 2012;26(3):398–407.

Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Karen D. Wagner, MD, PhD, at kwagner@psychiatrist.com.

See supplementary material for this article at PSYCHIATRIST.COM.

THE JOURNAL OF
CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: Cannabidiol for Treatment-Resistant Anxiety Disorders in Young People: An Open-Label Trial

Author(s): Maximus Berger, MD PhD; Emily Li, BPsychPsy; Simon Rice, PhD; Christopher G. Davey, MBBS, PhD; Aswin Ratheesh, MBBS, PhD; Sophie Adams, MBBS PhD; Henry Jackson, PhD; Sarah Hetrick, PhD; Alexandra Parker, PhD; Tim Spelman, PhD; Richard Kevin, PhD; Iain S. McGregor PhD; Patrick McGorry MBBS PhD; and G. Paul Amminger, MD, PhD

DOI Number: https://doi.org/10.4088/JCP.21m14130

List of Supplementary Material for the article

1. Table 1 — Adverse events
2. Figure 1 — CONSORT Diagram
3. Figure 2 — Mean plasma concentrations of CBD in participants who received maximum daily doses of 400mg, 600mg and 800mg, respectively.

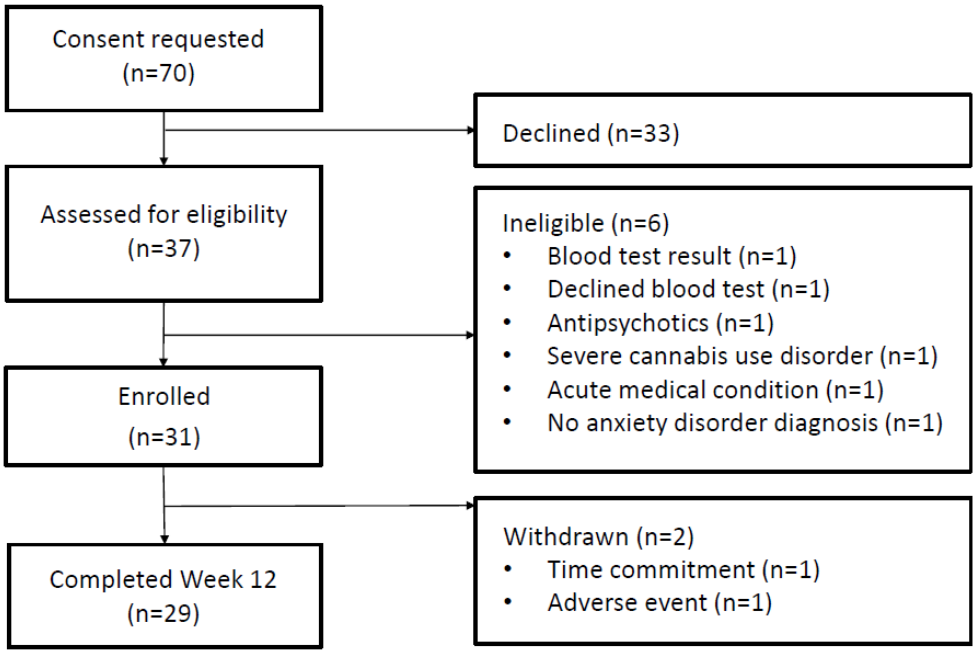
Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

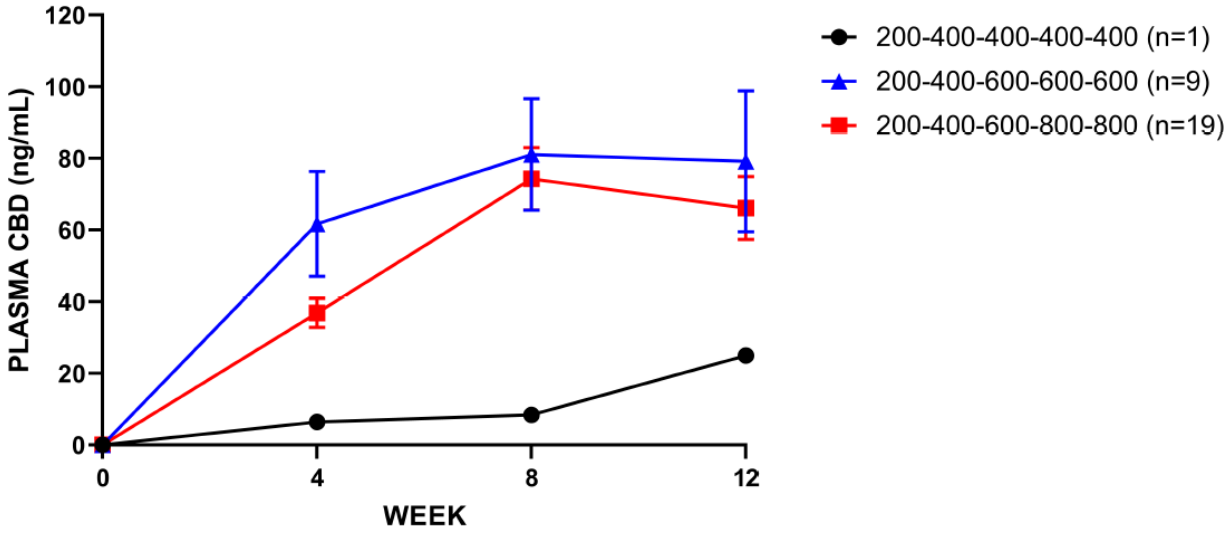
Supplementary Table 1 Adverse events

	All study participants (n=31)
Adverse event	**Frequency, n (%)**
Fatigue	8 (25.8%)
Low mood	3 (9.7%)
Hot flushes or cold chills	3 (9.7%)
Drowsiness	2 (6.5%)
Nausea	2 (6.5%)
Diarrhoea	2 (6.5%)
Dry mouth	2 (6.5%)
Insomnia	2 (6.5%)
Increased appetite	1 (3.2%)
Decreased appetite	1 (3.2%)
Urticaria	1 (3.2%)
Concentration difficulties	1 (3.2%)
Headache	1 (3.2%)
Dizziness	1 (3.2%)
Restlessness	1 (3.2%)
GI discomfort	1 (3.2%)
Muscle twitch	1 (3.2%)
Polyuria	1 (3.2%)
Hyperhidrosis	1 (3.2%)

Supplementary Figure 1 CONSORT Diagram



Supplementary Figure 2 Mean plasma concentrations of CBD in participants who received maximum daily doses of 400mg, respectively.



a Error bars represent SEM.